

REMARKS

Claims 1, 2, 4, 6, 7, 19, 20, 21 22, 23, and 26 are currently pending and under examination. Claims 1 and 26 are currently amended. Claims 3, 5, 8-18, 24, 25, and 27-41 remain withdrawn.

Applicants thank the Examiner for entering claim amendments submitted in the Amendment mailed October 13, 2004. Applicants thank the Examiner for withdrawing objections to the claims. Applicants thank the Examiner for withdrawing the rejection of Claims 2, 4, 6, 7, 19, 20, 21, 22, 23 under 35 U.S.C. §112, second paragraph.

Amendment of Claim 1

Claim 1 has been amended to recite that the claimed compound is “expressed in and secreted by” a mammalian host cell as a fully functional heterodimer as recited in the claim. The amendment is supported by the specification on page 5 at lines 21-22. The amendment is made solely for purposes of clarification and does not add new matter.

Claim Rejections Under 35 U.S.C. §112, second paragraph

Claim 26 remains rejected under 35 U.S.C. §112, second paragraph. Applicants have amended Claim 26 as previously suggested by the Examiner, to recite that the CH1 domain is “linked” to a histidine tag, thereby satisfying the requirements of 35 U.S.C. §112 and rendering the rejection moot.

Claim Rejections Under 35 U.S.C. §102

Claims 1, 2, 4, 6, 7, 19, 20, 21, 22, and 26 remain rejected under 35 U.S.C. §102(b) as allegedly anticipated by Müller *et al.* (1998, *FEBS Lett* 422:259-264), as allegedly evidenced by WO 97/01580. Applicants respectfully traverse this rejection for the reasons presented below.

To anticipate a claim, the reference must teach every element of the claim. “A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference.” MPEP § 2131, quoting *Verdegaal Bros. v. Union Oil Co. of California*, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987).

Müller *et al.* discloses the functional expression of bispecific antibodies in *E. coli* using plasmid constructs designed for recombinant expression of proteins in *E. coli* (*e.g.*, Materials and Methods, page 259 right column, to page 261, left column). Müller *et al.* disclose that “immunogenicity is expected to be low, since human sequences can be used for all components” in their *E. coli* expression system (page 259, last sentence of Introduction). Because Müller *et al.* does not set forth a multifunctional compound expressed in and

secreted by a mammalian host cell, Müller *et al.* does not anticipate the claims. Therefore, the rejection of independent Claim 1 and dependent claims 2, 4, 6, 7, 19, 20, 21, 22, and 26 under 35 U.S.C. §102(b) is improper and should be withdrawn.

Claim Rejections Under 35 U.S.C. §103

Claims 1, 2, 4, 6, 7, 19, 20, 21, 22, 23, and 26 remain rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Müller *et al.*, in view of Plückthun and Pack (1997, *Immunotechnology* 3:83-105). Müller *et al.* allegedly discloses a multifunctional compound with all the structural limitations of the rejected claims, for reasons given for the rejection under 35 USC §102(b) discussed above (OA page 8, lines 15-19). It is, however, admitted that Müller *et al.* does not teach the upper hinge region of human IgG3 (OA page 8, line 22). Plückthun and Pack allegedly teach the use of hinge regions, in particular the upper hinge from human IgG3 (OA page 9, lines 1-6). Based on these disclosures, it would allegedly “have been obvious to one of ordinary skill in the art to substitute the linkers of Müller *et al.*, with the upper hinge region of human IgG3 taught by Plückthun and Pack, to make a multifunctional compound.” (OA page 9, lines 10-13). Applicants respectfully traverse for the reasons presented below.

Criteria for establishing a prima facie case of obviousness

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference, or references when combined, must teach or suggest all the claim limitations. *See*, MPEP §§ 2142, 2143.

The combination of references does not teach or suggest all claim limitations

To establish *prima facie* obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. *In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974). Here, Müller *et al.*, discloses the functional expression of bispecific antibodies in *E. coli* using plasmid constructs designed for recombinant expression of proteins in *E. coli*. Müller *et al.* also disclose that “immunogenicity is expected to be low, since human sequences can be used for all components” in their *E. coli* expression system (page 259, last sentence of Introduction, cited at OA, page 8, lines 19-21). Applicants do not find any teaching in Plückthun and Pack that the *E. coli*-produced bispecific antibodies of Müller *et al.* can be expressed in and secreted by a mammalian host cell. Therefore, the cited

combination of references do not teach or suggest all the limitations of the claimed invention and a *prima facie* case of obviousness has not been established.

The combined references do not provide a suggestion or motivation to make the claimed invention

According to the MPEP, the prior art must suggest the desirability of the claimed invention. MPEP §2143.01 Obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. *In re Fine*, 837 F.2d 1071, 5 USPQ 2d 1596 (Fed. Cir. 1988); *In re Jones* 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). *See generally*, MPEP §2143. Here, there is no teaching, suggestion, or motivation in the Müller *et al.* reference or the Plückthun and Pack reference to combine the teachings of these references to produce the claimed invention.

The primary reference, Müller *et al.*, discloses the functional expression of bispecific antibodies in *E. coli* using plasmid constructs designed for recombinant expression of proteins in *E. coli*, and does not teach or suggest the claimed invention. Applicants do not find a teaching or suggestion in the secondary reference, Plückthun and Pack, to modify the *E. coli*-expressed bispecific antibodies of Müller *et al.* in such a way that these bispecific antibodies can be expressed in and secreted by a mammalian host cell.

Furthermore, the combination of Müller *et al.* and Plückthun and Pack teaches away from the claimed invention. Müller *et al.* discloses functional expression of bispecific antibodies in *E. coli*, noting that “immunogenicity is expected to be low, since human sequences can be used for all components” in their *E. coli* expression system (page 259, last sentence of Introduction, cited at OA, page 8, lines 19-21). Plückthun and Pack disclose “[p]rogress in *E. coli* expression technology” (page 83, Abstract), the convenience and advantages of using *E. coli* as compared with eukaryotes (page 87, left column, third paragraph), expression of recombinant antibody fragments in *E. coli* (Section 2.2. page 87, right column, to page 89, left column) and production of miniantibodies and diabodies by high cell density fermentation of *E. coli* (Section 6, page 99 right column, to page 100 left column). In summary, the cited combination discloses the advantages of functional expression of bispecific antibodies in *E. coli*. Applicants submit that such a disclosure teaches away from the claimed multifunctional compound expressed in and secreted by a mammalian host cell.

In conclusion, because the cited combination of references does not teach the claimed invention, and because there is no teaching, suggestion, or motivation in the cited references to combine the teachings of these references to produce the claimed invention, and further because the cited combination of references teaches away from the claimed invention, Applicants conclude that the cited references, alone or in combination, fail to meet the criteria for a *prima facie* case of obviousness and no *prima facie* case of obviousness has been established. Therefore, because no *prima facie* case of obviousness has been established, the rejection of Claims 1, 2, 4, 6, 7, 19, 20, 21, 22, 23, and 26 under 35 U.S.C. §103 is improper and should be withdrawn.

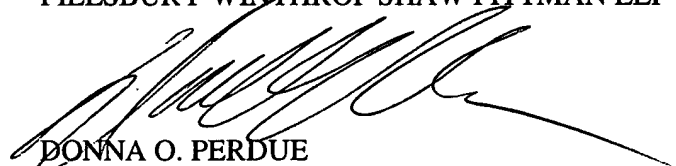
CONCLUSION

Claims 1, 2, 4, 6, 7, 19, 20, 21, 22, 23, and 26 are currently pending and under examination. Claims 1 and 26 are currently amended. Applicants submit that, in light of claim amendments and arguments submitted in this paper, all pending claims are now in condition for allowance.

Applicants believe that fees are due. Please charge any fees associated with the submission of this paper to Deposit Account Number 502212. The Commissioner for Patents is also authorized to credit any overpayments to the above-referenced Deposit Account.

Respectfully submitted,

PILLSBURY WINTHROP SHAW PITTMAN LLP



DONNA O. PERDUE

Reg. No. 51166

Tel. No. 858 509 4093

Fax No. 858 509 4010

Date: May 20, 2005
11682 El Camino Real
Suite 200
San Diego, CA 92130-2092
(619) 234-5000